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FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **2912-US**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): -- to be assigned -- 09/936509

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/08161	**28 March 2000 (28.03.2000)**	**02 April 1999 (02.04.1999)**

TITLE OF INVENTION

USE OF SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR FOR TREATMENT HEART FAILURE

APPLICANT(S) FOR DO/EO/US

F. Ann HAYES

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☐ Other items or information:

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR -- to be assigned) 09/936509	INTERNATIONAL APPLICATION NO. PCT/US00/08161	ATTORNEY'S DOCKET NUMBER 2912-US

24. The following fees are submitted:.		CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1000.00**	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$860.00**	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$710.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$690.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$860.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	5 - 20 =	0	x $18.00	**$0.00**
Independent claims	1 - 3 =	0	x $80.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**
TOTAL OF ABOVE CALCULATIONS =				**$860.00**
☐ Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**
SUBTOTAL =				**$860.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**
TOTAL NATIONAL FEE =				**$860.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☒				**$40.00**
TOTAL FEES ENCLOSED =				**$900.00**
			Amount to be: refunded	$
			charged	$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **09-0089** in the amount of **$900.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **09-0089** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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35,356
REGISTRATION NUMBER

September 12, 2001
DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of:
F. Ann HAYES

Docket No.: 2912-US

Group Art Unit: unknown

International Application No: PCT/US00/08161

Examiner: unknown

International Filing Date: March 28, 2000

For: USE OF SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR FOR TREATMENT HEART FAILURE

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, DC 20231

Prior to examination of the above referenced application, please enter the following amendment:

In the Specification:

At page 1 of the application, after the title but before the caption "BACKGROUND OF THE INVENTION" please insert the following paragraph:

-- This is a national phase patent application under 35 U.S.C. § 371, claiming priority from International Application No. PCT/US00/08161, filed March 28, 2000 and published in English on October 12, 2000 under PCT Article 21(2), which claims priority from United States Provisional Patent Application No. 60/127,588, filed April 2, 1999.--

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USE OF SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR FOR TREATMENT HEART FAILURE

BACKGROUND OF THE INVENTION

Chronic heart failure (CHF), also called "congestive heart failure," occurs when the heart is damaged from diseases such as high blood pressure, a heart attack, poor blood supply to the heart, a defective heart valve, atherosclerosis, rheumatic fever, heart muscle disease and so on. The failing heart becomes inefficient, resulting in fluid retention and shortness of breath, fatigue and exercise intolerance. CHF is defined by the symptom complex of dyspnea, fatigue and depressed left ventricular systolic function (ejection fraction < 35-40%), and is the ultimate endpoint of all forms of serious heart disease.

Treatment of CHF has been directed primarily to prolonging the patient's life, although the benefits from treatment generally is assessed through improvement in other areas. For example, a reduced degree of dyspnea or improvement in performance in a standardized walking test have a substantial positive impact on the lifestyle of patients who live with this disease. An increased ejection fraction, which can be measured by echocardiogram or by multigated radionuclide ventriculography (MUGA), is another indicator of a successful treatment regimen.

It has been proposed that the cytokine TNFα may contribute to the progression of heart failure by exerting direct toxic effects on the heart and the circulation (see, e.g., Yokoyama et al., *J. Clin Invest* 92:2303-2312, 1993; Torre-Amione et al., *Circulation 93*: 704-711, 1996. TNFα is a pleiotropic cytokine that is produced by the heart under certain forms of stress (Kapadia et al., *J. Clin Invest 96*:1042-1052, 1995b; Kapadia et al., *Circ Res 81*: 187-195, 1997). For example, patients with various types of heart disease have elevated levels of circulating TNFα, and the levels of TNFα have been shown to increase with disease progression (see, e.g., Maury et al., *J. Intern Med 225*: 333-336, 1989; Levine et al., *N Engl J Med 323*: 236-241, 1990; McMurray et al., *Br Heart J 66*: 356-358, 1991; Han et al., *JACC 19(3)*: 207A Abstract #768-6, March 1, 1992; Matsumori et al., *Br Heart J 72*: 561-566 1994b; Satoh et al., *J. Am. Coll. Cardiol. 29*: 716-724, 1997; Seta et al., *J. Cardiac Failure 2*: 243-249, 1996; Torre-Amione et al., *Circulation 93*:704-711, 1996b).

Pathophysiologically relevant peripheral and/or elevated intramyocardial levels of TNFα are sufficient to mimic many aspects of the heart failure phenotype, including left ventricular dilation, left ventricular dysfunction, as well as activation of the fetal gene program (Suffredini et al., *N Engl J Med 321*:280-287, 1989; Hegewisch et al., *Lancet 2*:294-295, 1990), hence it has been suggested that TNFα plays a contributory role in the pathogenesis of heart failure (see, e.g., Seta et al., *J. Cardiac Failure 2*:243-249, 1996).

It has been suggested that suppression of TNFα might benefit CHF patients (e.g., McMurray et al., *Br Heart J 66*:356-358, 1991), and many studies have provided support for this proposal. For example, TNFα has been shown in isolated hamster heart to inhibit contractility (Finkel et al., *Science 257*:387-389, 1992). In mice, antibodies against TNFα were effective in ameliorating the severity of artificially-induced heart disease (Smith et al., *Circ Res 70*: 856-863, 1992). In another study, TNFα-induced depression in left ventricle function in rats was partially reversed by administering the TNFα antagonist TNFR:Fc (Bozkurt et al., *Circulation 97(14)*: 1382-1391, 1998), and in yet a different study, TNFR:Fc was shown to suppress the negative inotropic effect of TNF in cultured myocytes (Kapadia et al., *Am J Physiol 37*:H517-H525, 1995a). Others demonstrated that TNFR:Fc could reduce burn-induced myocardial dysfunction in guinea pigs (Giroir et al., *Am J Physiol 267 (Heart Circ Physiol 36)*:H118-H125, 1994). Another study showed that vesnarinone, an agent used to treat CHF, could suppress lipoprotein-induced TNFα production human blood cells *in vitro* (Matsumori et al., *Circulation 89*:955-958, 1994a).

A small group of human CHF patients were given a single dose of TNFR:Fc, and fourteen days later exhibited decreased levels of circulating TNFα, increased ability to exercise, and improved symptomology (Deswal et al., Abstract #472, American Heart Association 70th Scientific Session, *Circulation 96(8Suppl.)*, 1997 I323). In addition, the TNFα suppressor pentoxifylline reportedly induces improved left ventricle function concomitant with decreased levels of serum TNFα levels in patients with idiopathic dilated cardiomyopathy (Skudicky et al., American Heart Association Meeting, Abstract No. 3415 November, 1998; Sliwa et al., *Lancet 351*: 1091-1093, 1998). The treatment of various heart diseases with TNFα antagonists is disclosed also in a number of U.S. patents and in several published patent applications (see, e.g., U.S. 5,594,106; U.S. 5,629,285; U.S. 5,691,382; U.S. 5,700,838; U.S. 5,886,010; WO 91/15451; WO

94/10990; WO 95/19957; WO 96/21447; WO 97/30088; EP 0 453 898 B1; EP 0 486 809 A2; EP 0 626 389 A1).

TNFα binds to cells through two membrane receptor molecules having molecular weights of approximately 55 kDa and 75 kDa (p55 and p75). In addition to binding TNFα, these same receptors mediate the binding to cells of TNFβ, which is another cytokine associated with inflammation. TNFβ, also known as lymphotoxin-α (LTα), shares structural similarities with TNFα (Cosman, *Blood Cell Biochemistry 7*: 51-77, 1996).

Although progress has been made in devising effective treatment for CHF in human patients, improved medicaments and methods of treatment are needed.

SUMMARY OF THE INVENTION

The invention provides methods for treating chronic heart failure by repeatedly administering a recombinant TNFR:Fc, more specifically, etanercept, for a period of time sufficient to induce a sustained improvement in the patient's condition.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 illustrates the improved NYHA classification that was observed in the patients who received etanercept in the study described in Example 1.

FIGURES 2A and 2B illustrate the improved left ventricular ejection fraction by MUGA in the patients who received etanercept in the study described in Example 1.

FIGURE 3 illustrates the improved Quality of Life (MLWHF) that was observed in patients who received etanercept in the study described in Example 1.

FIGURE 4 illustrates the end-of-study clinical composite score distributions for the patients who participated in the study described in Example 1.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides methods of treating chronic heart failure (CHF) that involve administering to a CHF patient a TNFα antagonist that is capable of inhibiting the binding of TNFα to a TNFα receptor. In a preferred embodiment of the invention, the TNFα antagonist is one that mimics the 75 kDa TNFR and that binds to TNFα in the patient's body. Once bound to the antagonist, the TNFα is prevented from binding its

natural receptor, and thus cannot manifest its biological activities. A TNFα antgonist suitable for use in treating CHF is recombinant TNFR:Fc (hereafter referred to as "TNFR:Fc" or "etanercept"). Etanercept is currently sold by Immunex Corporation under the trade name ENBREL,® and is a dimer of two molecules of the extracellular portion of the p75 TNFα receptor, each molecule consisting of a 235 amino acid polypeptide that is fused to a 232 amino acid Fc portion of human IgG_1. In addition to etanercept, the use of other soluble mimics of the p75 molecule for treating CHF are within the scope of the invention.

To treat CHF, TNFR:Fc or another TNFα-binding mimic of p75 is administered repeatedly to a CHF patient in an amount and for a time sufficient to induce a sustained improvement over baseline in at least one indicator that reflects the degree of the patient's heart disease. For purposes of this invention, an improvement is considered "sustained" if the patient exhibits the improvement on at least two occasions separated by at least four weeks. A sustained degree of improvement generally is obtained by repeatedly administering TNFR:Fc over a period of at least a month, e.g., for one, two, or three months or longer.

Various indicators that reflect the patient's degree of heart failure may be assessed for determining whether the amount and time of the treatment is sufficient. The baseline value for the chosen indicator or indicators is established by examination of the patient within about 60 days prior to administration of the first dose of the etanercept or other TNFα-binding molecule.

If administered by injection, the effective amount of TNFR:Fc ranges from 1-20 mg/m^2, and preferably is about 5-12 mg/m^2. Alternatively, a flat dose may be administered, whose amount may range from 5-100 mg/dose. An exemplary range for a flat dose is about 20-30 mg per dose. In one embodiment of the invention, a flat dose of 25 mg/dose is repeatedly administered by subcutaneous injection. If a route of administration other than injection is used, the dose is appropriately adjusted in accord with standard medical practices.

Regardless of route of administration, it should be understood that the specific dose level and frequency of administration for a given patient may depend upon a variety of factors such as their age, body weight, general health, sex, diet, time of administration,

other drugs being concurrently administered, side-effects the patient may experience and the severity of their heart disease.

In one of the preferred embodiments of the invention, chronic heart failure is treated by administering to the patient by subcutaneous injection a dose of TNFR:Fc at 5 mg/m^2 or 12 mg/m^2 per dose up to a maximum of 25 mg per dose at least two times per week for a time sufficient to induce a sustained improvement over baseline of one of the following indicators: i) left ventricular ejection fraction; ii) New York Heart Association class; and iii) clinical composite score.

In one embodiment of the invention, the sufficiency of treatment is determined by evaluating the patient for an improvement in their left ventricular function. A sufficient degree of improvement with respect to this indication is obtained by repeatedly administering a dose of TNFR:Fc or other TNFα-binding molecule until the patient manifests an at least 5%, or more preferably an at least 10% increase over baseline in left ventricular ejection fraction. The left ventricular ejection fraction can be determined by any suitable means, such as echocardiogram or by multigated radionuclide ventriculography (MUGA).

In another embodiment, the treatment is regarded as suffient when it has induced a sustained improvement in the recipient's clinical composite score. A patient's clinical composite score is designated as "improved," "unchanged," or "worse" relative to baseline according to the following definitions. "Worse" means that the patient (1) died; (2) has had a hospitalization related to CHF; (3) has a worse NYHA functional classification (e.g., degenerates from Class I to Class II, from Class II to Class III or from Class III to Class IV); or (4) indicates that he or she feels moderately or markedly worse in a subjective patient global assessment after 24 weeks of treatment. The patient global assessment consists of the patient's response when asked whether their heart failure is: markedly better; moderately better; slightly better; unchanged; slightly worse; moderately worse; or markedly worse. An "improved" clinical composite score means that NYHA class is decreased by at least one class level (e.g., from Class III to Class II) *and* that the patient's global assessment of CHF is moderately or markedly improved. If the patient's clinical composite score is neither worse nor improved according to the foregoing criteria, then the clinical composite is scored as "unchanged." If clinical composite score is used as an indicator of the patient's degree of heart failure, a designation of "improved" is

considered indicative that the time and amount of the treatment with TNRF:Fc is sufficient.

In another embodiment of the invention, the indicator used to assess the patient's degree of heart failure is NYHA class of heart disease, and the amount and time of treatment is considered sufficient if the treatment has induced the patient's NYHA class to improve by at least one level, e.g., from Class II to Class I, from Class III to Class II, or from Class IV to Class III.

In yet another embodiment of the invention, the amount and time of treatment with TNFR:Fc is determined to be sufficient when the treatment has induced an increase in the patient's quality of life as scored by the Minnesota Living with Heart Failure Quality of Life Questionnaire (MLWHF Scale). Preferably, the treatment will induce an improvement of at least 19%, or more preferably at least 25% over baseline in the patient's MLWHF score.

Although a patient's degree of CHF after treatment may appear improved according to one or more of the above-discussed indices of heart condition, it should be understood that treatment with TNFR:Fc may be continued after the patient has shown improvement, and may be continued indefinitely if the patient's physician determines that this would be beneficial to the patient. Long-term treatment may be administered at the original dose or at a reduced maintenance dose. Moreover, if the treatment is discontinued for any reason, the treatment may be resumed if the patient's condition should worsen.

In addition to subcutaneous injection, any other efficacious route of administration may be used to therapeutically administer TNFR:Fc or other TNFα antagonist comprising a TNF receptor. TNFR:Fc can be administered to a CHF patient, for example, via intra-articular injection, intramuscular injection, intraperitoneal infusion or bolus injection, continuous infusion into a vein or artery, intrathecal or subdural injection, sustained release from implants, aerosol inhalation, suppository, oral preparations, such as tablets, capsules, pills or syrups, transdermal patch, biodegradable microcapsules or other suitable techniques, such as *in vivo* or *ex vivo* transfection of the patient's cells with recombinant DNA expressing a TNFR:Fc polypeptide.

Typically, TNFR:Fc is administered in the form of a composition comprising purified recombinant protein in conjunction with physiologically acceptable carriers,

excipients or diluents. Such carriers should be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the TNFR:Fc with buffers, antioxidants such as ascorbic acid, low molecular weight polypeptides (such as those having fewer than 10 amino acids), proteins, amino acids, carbohydrates such as glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. Preferably, the TNFR:Fc is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in standard dosing trials, and may vary according to the route of administration that is chosen. In accordance with appropriate industry standards, preservatives may also be added, such as benzyl alcohol. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth.

The compositions described herein preferably are administered at least one time per week. In a preferred embodiment of the invention, TNFR:Fc is administered at least two times per week, and in another preferred embodiment, it is administered at least three times a week.

Etanercept is a dimeric TNFR that competes for TNFα with the receptors on the cell surface, thus inhibiting TNFα from binding to the cell. In contrast to many other types of TNF inhibitor, inhibitors comprising a TNFR are capable also of binding to the inflammatory cytokine LTα. Thus, TNRF:Fc has the capacity to suppress the binding of LTα to its natural receptors, which may contribute to the potency of TNFR:Fc.

The following examples are provided to illustrate the advantages of the invention, and are not intended in any way to limit the scope of the disclosure.

EXAMPLES

Example 1. Evaluation of TNFR:Fc in patients with chronic heart failure.

Forty-seven patients with Class III-IV heart failure were evaluated in a Phase I/II randomized, placebo controlled double-blinded study to determine whether the long-term subcutaneous biweekly administration of etanercept (recombinant TNFR:Fc) was safe in this patient population and whether efficacy could be documented. Two dose levels of TNFR:Fc were evaluated in this study. To assess improvement in the patient's degree of

heart disease, parameters assessed at the end of the study included ventricular function (as indicated by left ventricular ejection fraction), NYHA class, quality of life, clinical composite score, as well as numerous other measures that reflected the patient's degree of heart disease. Baseline values for all of these parameters were established prior to administration of the first dose of etanercept or placebo.

Efficacy was evaluated by assessing clinical and laboratory indices for evidence of improvement in: NYHA class; serum levels of TNFα; left ventricular ejection fraction by MUGA; left ventricular volume by MUGA; left ventricular ejection fraction and dimension and cardiac output by 2-D echo; exercise tolerance by six minute walk test; quality of life (visual analog and Minnesota Living with Heart Failure); global assessment of heart failure (VAS), including patient global assessment and physician global assessment; and heart size. At the beginning and at the end of the study (days 1 and 84), serum was collected for determination of TNFα, TNFR:Fc antibodies, IL-1α, IL-6, IL-10, norepinephrine, plasma renin activity and atrial natriuretic factor levels. The study also tracked the degree to which the two study groups required hospitalization for any cause. Values measured during and after the study were compared to baseline values.

The walking test is a simple objective guide to disability in patients with chronic heart failure. The tests were carried out in a level corridor and each patient was instructed prior to the test to cover as much ground as possible in 6 minutes.

Classification according to the New York Heart Association (NYHA) criteria was performed as follows:

CLASS I

No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.

CLASS II

Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

CLASS III

CLASS IIIA: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

CLASS IIIB: Marked limitation of physical activity. Comfortable at rest, but minimal exertion causes fatigue, palpitation or dyspnea.

CLASS IV

Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency present at rest. If any physical activity is undertaken, discomfort is increased.

The above criteria were derived from the Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of the Heart and Great Vessels (8th Edition, Boston: Little, Brown and Co., 1979), but were modified to add Classes IIIA and IIIB.

Clinical composite was assessed for each patient at the beginning and end of the study. After the clinical composite assessment, each patient was classified as "better," "worse," or "unchanged." The clinical composite for each patient was considered to be improved, unchanged or worse at the end of the study based on the following definitions:

Worse:

1. died;
2. had a CHF hospitalization;
3. has worse NYHA functional classification at 24 weeks;
4. has indicated moderately or markedly worse on the patient global assessment at 24 weeks.

Patients were considered "worse" if events 1 and 2 above occurred within 24 weeks following randomization or if events 3 or 4 occurred at 24 weeks. A patient was considered to have had a CHF hospitalization if he/she was hospitalized for or with worsening heart failure (admission of at least 1 day defined as a change in dates) and received intravenous diuretics, vasodilators or positive inotropic drugs for the treatment of heart failure.

Improved:

NHYA class was improved; and

Overall assessment of CHF (judged by patient global assessment) was judged to be moderately or markedly improved.

Unchanged:

If at 24 weeks, the patient was neither worse nor improved, then he/she was classified as "unchanged."

The Minnesota Living with Heart Failure Quality of Life scale was assessed by presenting patients with the following questionnaire (Rector et al., 1983, 1987 and 1992):

These questions concern how your heart failure (heart condition) has prevented you from living as you wanted during the last month. The items listed below describe different ways some people are affected. If you are sure an item does not apply to you or is not related to your heart failure then circle 0 (No) and go on to the next item. If an item does apply to you, then circle the number rating how much it prevented you from living as you wanted. Remember to think about ONLY THE LAST MONTH.

	Did your heart failure prevent you from living as you wanted during the last month by:	No	Very Little				Very Much
1.	Causing swelling in your ankles, legs, etc.?	0	1	2	3	4	5
2.	Making you sit or lie down to rest during the day?	0	1	2	3	4	5
3.	Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4.	Making your working around the house or yard difficult?	0	1	2	3	4	5
5.	Making your going places away from home difficult?	0	1	2	3	4	5
6.	Making your sleeping well at night difficult?	0	1	2	3	4	5
7.	Making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8.	Making your working to earn a living difficult?	0	1	2	3	4	5
9.	Making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10.	Making your sexual activities difficult?	0	1	2	3	4	5
11.	Making you eat less of the foods you like?	0	1	2	3	4	5
12.	Making you short of breath?	0	1	2	3	4	5
13.	Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14.	Making you stay in a hospital?	0	1	2	3	4	5
15.	Costing you money for medical care?	0	1	2	3	4	5
16.	Giving you side effects from medications?	0	1	2	3	4	5
17.	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18.	Making you feel a loss of self-control in your life?	0	1	2	3	4	5
19.	Making you worry?	0	1	2	3	4	5
20.	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21.	Making you feel depressed?	0	1	2	3	4	5

The numbers 0-5 assigned to each of the 21 answers were added together to obtain the patient's MLWHF score.

Patient enrollment

Patients who were eligible for enrollment met the following criteria: male or female between 18 and 75 years of age; not pregnant if female; willing to practice contraception during the trial; NYHA Class III or IV (see below); ejection fraction ≤ 35% (as assessed by radionuclide ventriculography within 60 days prior to randomization); receiving standard and stable (1 month) triple therapy for heart failure (angiotensin converting enzyme (ACE) inhibitor and diuretics); able to walk a minimum of 100 m during a standard 6 minute corridor walking test. Patients with severe infections were excluded. All patients provided informed consent.

Patients were permitted to continue all maintenance cardiac medications while enrolled in this study, and the dose level of etanercept for each enrolled patient remained constant throughout the study. Basic demographic information was collected from all enrolled patients, and were found to be comparable in all three treatment groups.

Dosing regimen

Recombinant human TNFR:Fc (etanercept) that was used in this study was obtained from Immunex Corporation. The gene fragments encoding the etanercept polypeptides were expressed in a Chinese hamster ovary (CHO) expression vector.

TNFR:Fc was supplied as a sterile lyophilized powder containing 10 mg or 25 mg TNFR:Fc; 40 mg mannitol, USP; 10 mg sucrose, NF; and 1.2 mg tromethamine (TRIS), USP per vial. One group of patients received 5 mg/m^2 (max. 10 mg) of etanercept, another group received 12 mg/m^2 (max. 25 mg) of etanercept and a third group received a placebo. Vials of etanercept were reconstituted by aseptic injection of 1.0 mL Bacteriostatic Water for Injection, USP, (containing 0.9% benzyl alcohol). The reconstituted solution was not filtered during preparation or prior to administration. If storage was required, the reconstituted solutions were stored at 2-8°C (36-46°F) in the original vial or in a plastic syringe for a period of no longer than 28 days.

Study drug was dispensed in syringes to patients to be self-administered at home. Study drug was given twice weekly at approximately the same time of day, and the site for injection rotated to a different site with each subcutaneous injection.

Patient Evaluations included:

Day 1 of Study Drug (prior to administration of drug)

Vital signs were taken for each patient, including blood pressure, heart rate and respiratory rate. In addition, each patient received a cardiopulmonary examination.

During study and at end of study (day 84)

Vital signs (blood pressure, heart rate, respiratory rate) were taken on days 28, 56 and 84; complete physical examinations and interim cardiac history were done on day 84; cardiopulmonary examinations were done on days 28, 56 and 84; 2-D echo/Doppler assessments were done on days 28 and 84. At the end of the study (day 84), the following tests were done: MUGA; CXR; ECG; CBC; differential; platelets; creatinine; SGOT/SGPT. In addition, AEs were recorded from patient diary (every visit). At days 28, 56 and 84, NYHA functional classification, 6 minute walk distance and Quality of Life questionnaires were done.

All subjects who received at least one dose of study drug were evaluated for safety (vital signs, physical exams, hematology profile, blood chemistry profile, hemodynamic parameters, urinalysis, antibody formation against TNFR:Fc, symptom/toxicity assessment).

Measurements of LV function

Clinical and laboratory indices of biological activity were assessed for evidence of improvement in left ventricular ejection fraction by MUGA, left ventricular volume by MUGA and left ventricular ejection fraction and dimension and cardiac output by 2-D echo.

Results

Doses of 5 and 12 mg/m^2 were well tolerated in CHF patients. Adverse events were consistent with this population and were equally distributed amongst the treatment groups, including the placebo group.

As illustrated in FIGURE 1, a shift to a lower NYHA classification was observed in patients who received either dose of etanercept, the shift being more pronounced in the group who received the higher dose. FIGURES 2A and 2B illustrate that, as compared with the placebo, the patients who received etanercept exhibited improved left ventricular ejection fraction by MUGA. Eight to thirteen percent of the etanercept recipients but none of the placebo group showed an at least 10% improvement in LV ejection fraction

(see FIGURE 2B). FIGURE 3 shows further that the patients who received etanercept exhibited an improved Quality of Life (MLWHF-physical dimension) as compared with the placebo group, and FIGURE 4 illustrates that a greater proportion of the etanercept recipients as compared with the placebo group ended the study with an improved clinical composite score. Furthermore, the benefits illustrated in FIGURES 2A, 2B, 3 and 4 showed a dose-dependency that is consistent with the benefits being attributable to the etanercept.

As illustrated here, etanercept dosed for three months was well tolerated in patients with CHF and induced an overall improvement in their condition, as manifest by a number of indicators, including NYHA classification, clinical composite score, ventricular function and quality of life scores. These changes were more pronounced in the 12 mg/m^2 group, but were apparent also in the 5 mg/m^2 group.

Example 2. Multi-site randomized TNFR:Fc study in CHF patients

A double-blind, placebo controlled study will be conducted in multiple sites and will involve 900 patients with heart failure, stratified based upon baseline β-blocker use and NYHA functional class. This clinical trial will evaluate the efficacy of two dosing regimens of etanercept subcutaneous (SC) injections and placebo in patients with Class II-IV chronic heart failure (CHF). Endpoints will include the clinical composite score at 24 weeks and a combined analysis of all-cause mortality and morbidity (CHF hospitalizations). Specific covariates will be examined, including left ventricular ejection fraction (LVEF), etiology of heart failure, age, and gender. Baseline values for all study parameters will be determined by examining each patient within about 60 days prior to administration of the first dose of etanercept. Unless otherwise indicated, values for various indicators of heart disease (e.g., NYHA class, serum TNFα, walking test, left ventricle function, clinical composite score, MLWHF score, etc.) will be be determined as described above in Example 1. The etanercept employed for this study and its preparation for injection is described above in Example 1.

The data obtained will be analyzed in combination with data from a second trial of etanercept whose design will be similar to this 900 patient clinical trial. A time to first event analysis will be included, and study duration will depend on event rate. The study will continue at least until all enrolled patients have completed 24 weeks of treatment, and

may continue for up to one year longer in order to observe the targeted number of events (389 events, including either mortality or CHF hospitilizations) for the combined patients in the two studies.

At 24 weeks, the following will be assessed and compared with baseline: changes in left ventricular ejection fraction; changes in global assessment of progress assessed by the investigator; and changes in Minnesota Living with Heart Failure (MLWHF) Scale, as based on the MLWHF Questionnaire. Additional measurements will include: characterization of the pharmacokinetics (and pharmacodynamics) of etanercept in a subset of patients with CHF; evaluation of the overall economic impact of the use of etanercept in patients with Class II-IV CHF by conducting a cost effectiveness analysis through the relative (compared with placebo) use of medical care; and safety analysis.

To be included in this study, patients must meet the following criteria: 18-85 years of age; agree to use contraception throughout the study; exhibit NYHA Functional Class II-IV CHF; have a ventricular ejection fraction ≤ 30%; receiving stable (> 2 weeks) therapy for heart failure; 6-minute walk distance > 50 meters and < 375 meters **or** < 425 meters plus hospitalization for CHF within previous 6 months. Patients included in the study must be receiving therapy for heart failure including a diuretic and an ACE inhibitor (unless there is a history of ACE intolerance or a contraindication to use), and may also be receiving digoxin, angiotensin II antagonist, beta blocker, amiodarone, nitrates, and hydralazine, but these medications must have been constant for 2 weeks prior to randomization. Female patients may not be pregnant or lactating. Throughout the study, treatment with antiarrhythmic drugs and nonsteroidal anti-inflammatory drugs will be avoided.

A detailed medical history will be taken prior to study entry, which will include ischemic heart disease; myocardial infarction; history of arryghmia; hypertension; dilated cardiomyopathy; CHF history, including NYHA class; and history of recent hospitilizations. Patients during the study will be evaluated for vital signs and physical examination, cardiopulmonary assessment, routine labs, antibody formation against etanercept, and adverse events. Laboratory assessments will be performed at screening and at weeks 2, 4, 12 and 24.

To characterize the pharmacokinetics of etanercept, serum samples will be collected from a subgroup of 200 randomly selected patients at Day 1 and at the end of

Weeks 4, 12, and 24. Of the 200 patients, 40 patients from selected sites also will have serum for etanercept concentrations collected on Days 3, 5, 7, and 9. The concentration data will be combined with demographic and dose administration data. In addition, covariates potentially responsible for variability in pharmacokinetics will be examined, including weight, gender, ethnic background, age, and concomitant medication administration.

Dosing regimen. Starting on Day 1 of the double-blind period, three groups each containing 300 patients will receive by SC injection:

1) 25 mg of etanercept twice a week and placebo once a week;
2) 25 mg of etanercept three times a week; or
3) placebo three times a week.

Following completion of Week 24 of study drug or immediately after premature discontinuation (EOS), patient evaluations will include: NYHA classification; physician global assessments; changes in the Minnesota Living with Heart Failure (MLWHF) Scale and VAS; vitals signs including weight; limited physical exam; cardiopulmonary exam; review AEs and concomitant medications; routine laboratory; serum/plasma bank (for markers of heart failure); etanercept antibodies; chest x-ray; and change in left ventricular ejection fraction (MUGA) in 300 patients. After week 24, patients will continue to be evaluated every 12 weeks for physical condition, NYHA classification, laboratory tests, and anti-etanercept antibodies.

What is claimed is:

1. A method of treating chronic heart failure in a patient having chronic heart failure, said method comprising administering to the patient by subcutaneous injection a dose of TNFR:Fc at 5 mg/m^2 or 12 mg/m^2 per dose up to a maximum of 25 mg per dose at least two times per week for a time sufficient to induce a sustained improvement over baseline of an indicator selected from the group consisting of left ventricular ejection fraction, New York Heart Association class and clinical composite score, wherein the improvement is considered sustained if the patient exhibits the improvement on at least two occasions separated by at least four weeks.

2. A method according to Claim 1, wherein the sustained improvement is an at least 10% improvement over baseline in left ventricular ejection fraction.

3. A method according to Claim 1, wherein the sustained improvement is an improvement of at least one level in New York Heart Association class.

4. A method according to Claim 1, wherein the sustained improvement is an improvement in clinical composite score.

5. A method according to Claim 1, wherein the TNFR:Fc is administered three times per week.

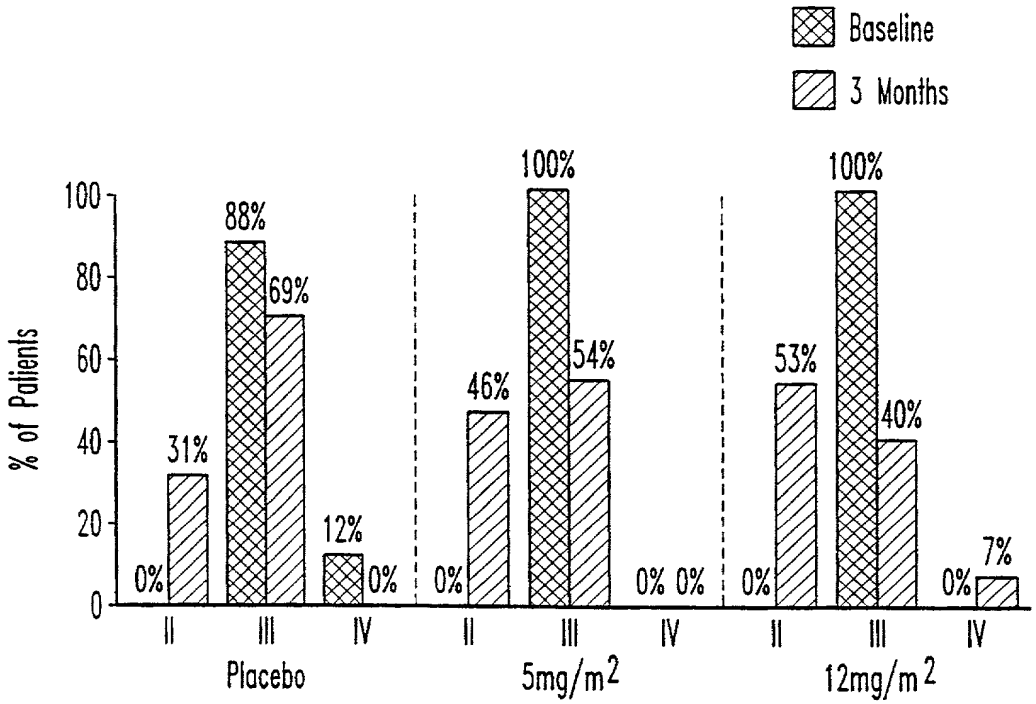

Fig. 1

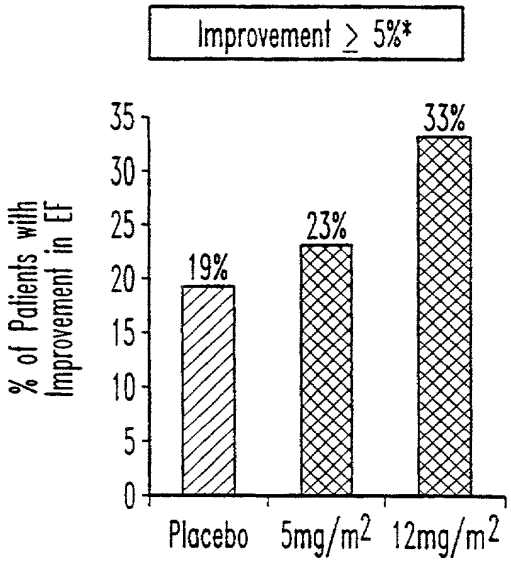

Fig. 2A

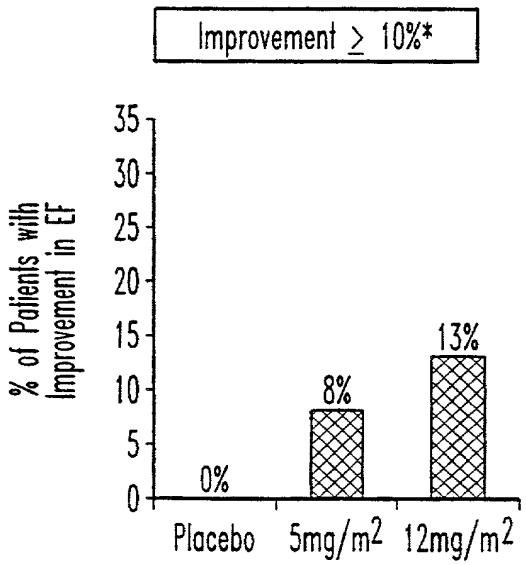

Fig. 2B

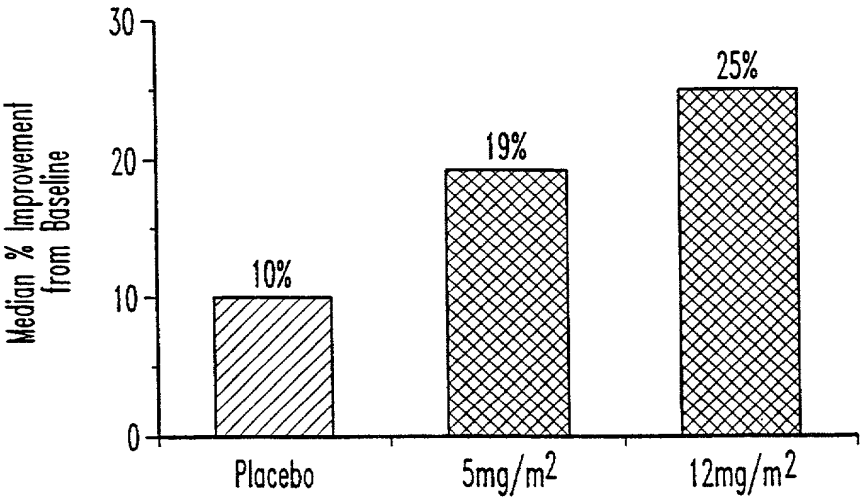
Median % Improvement from Baseline
30
20
10
0
10%
19%
25%
Placebo
5mg/m2
12mg/m2

Fig. 3

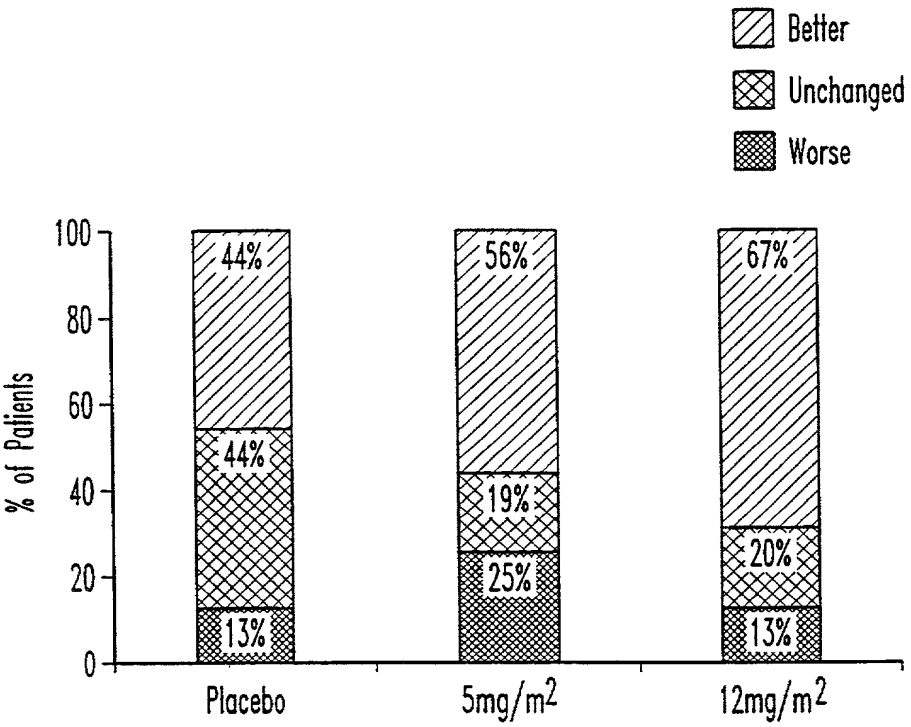
Better
Unchanged
Worse
% of Patients
100
80
60
40
20
0
44%
44%
13%
56%
19%
25%
67%
20%
13%
Placebo
5mg/m2
12mg/m2

Fig. 4

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-00

Signature F. Ann Hayes Date 9-10-01

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Immunex Corporation Docket No.: 2912-US

DECLARATION

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe that I am an original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR FOR TREATMENT HEART FAILURE

the specification of which

☒ is attached hereto.

OR

☐ was filed on as United States Application No. or PCT International Application No. .

I hereby state that I have reviewed and understand the contents of said specification, including the claims. I acknowledge the duty to disclose information that is known to me and material to patentability of the subject claimed invention in accordance with 37 C.F.R. §1.56.

☒ I hereby claim the benefit under 35 U.S.C. §120 of the United States application(s) and PCT international application(s) designating the United States that are listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) or PCT international application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application.

Application No.	Filed
PCT/US00/08161	March 28, 2000

☒ I hereby claim the benefit under 35 U.S.C. §119(e) of the United States provisional patent application(s) listed below:

Application No.	Filed
60/127,588	April 2, 1999
